REMARKS

Status of the Claims and Formal matters.

Claims 193, 194, 214-221 and 223-230 are pending. The withdrawn claims 157-192 and 195-213 were canceled without prejudice. Applicants reserve the right to file a divisional application for the cancelled subject matter. Claim 193 was amended to clarify that the invention is directed to a method for significantly increasing the recovery of radioactivity of a radiopharmaceutical composition of limited solubility. These amendments are supported throughout the specification, particularly at Example 23 and paragraph [0023] of the specification as filed. Claim 221 was amended to delete the language "and derivatives" solely to expedite prosecution and Claim 222 was cancelled without prejudice. Claim 217 was amended to correct the spelling of "radiopharmaceutical". Finally, contrary to the Examiner's assertion, claim 227 has a correct spelling of the word "method". Thus, no new matter has been added.

The Examiner found our traversal of the restriction requirement unpersuasive and made it final. Further, the Examiner found that claims 193, 194, 214, 215, 217 and 219-230 read on the elected species. Claims 157-192, 195-213, 216 and 218 are now withdrawn as being drawn to a non-elected invention/species. Specifically, claims 157-192, 195-213 and 230 are directed to the non-elected invention and claims 216 and 218 are directed to the non-elected species.

The species of claim 217 was searched and no art was found. Further, the search was expanded to "to the species disclosed in Liu et al (US 2002/0122768) and Gustafson et al (British Journal of Industrial Medicine, 1985, Vol. 42, page 591-595).

In order to advance prosecution, specification is amended at page 48, lines 6, 13, 19, 25 and 31 to remove the question mark before the wavelength.

Rejections under 35 U.S.C. §112 first paragraph-written description requirement.

Claims 193, 194, 214, 215, 217 and 219-230 were rejected for alleged failure to comply with the written description requirement. The Examiner contends that "[t]he instant application

does not sufficiently describe the invention as it relates to the reaction reactants and products that are compatible with the instant invention. Specifically, one cannot ascertain if Applicant's invention will work with ALL reactions that produce a radiopharmaceutical. In addition, Applicant is reminded that while a generic claim may define the boundaries of a vast genus of radiopharmaceuticals, the question may still remain as to whether or not the specification, including original claim language, demonstrates that Applicant has invented species sufficient to support a claim to a genus. In this particular instance, the problem is especially acute since the claims are directed to a desired result without describing the reactants without describing species that achieved the desired result." (Office Action, page 5). Applicants respectfully traverse.

Applicants therefore respectfully state that the test for written description under 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having ordinary skill that Applicants had possession of the subject matter later claimed. *In re Kaslow*, 217 U.S.P.Q. 1089 (Fed. Cir. 1983), *See also*, MPEP, §2163.02.

Applicants further stress that whether the specification shows that Applicant is in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. "Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient" MPEP, §2163.02; *See also Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Applicant's respectfully point out that instant specification describes every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Examiner's attention is respectfully directed to the amended claims related to a method of significantly increasing

recovery of radioactivity from a reaction that produces a radiopharmaceutical composition of limited solubility by adding benzyl alcohol to the reaction mixture that produces the radiopharmaceutical of limited solubility or to the stabilizer solution added to a radiolabeled chelate of limited solubility.

As explained below, Applicant's invention is directed to using benzyl alcohol to increase the recovery of the radioactivity in a given radiopharmaceutical composition; thus Examiner's interpretation of the invention at page 12 ("the amount of radioactivity of the radiopharmaceutical increases anytime benzyl alcohol is present in the mixture") is not correct.

The claimed invention solves the problem of precipitation and deposition of radioactivity on the walls of a vial that can occur over time with radiopharmaceuticals of limited solubility. When the radiopharmaceutical is removed from the vial the precipitated portion may remain stuck to the vial walls. Thus, if 25% of the radioactivity in a radiopharmaceutical composition containing 200mCi remains deposited on the wall of the vial, only 150 mCi can be recovered, reducing the effective dose.

As set forth in paragraph [0023] and Example 23 of the published application, Applicants unexpectedly found that addition of benzyl alcohol solubilizes radiopharmaceutical compositions of limited solubility so they remain dissolved in the reaction solution and thus significantly more of these solutions (and the radioactivity they contain) can be recovered from the reaction vial. Indeed, in Example 23, in the absence of benzyl alcohol only 85.3 % of the radioactivity could be recovered from the vial, while addition of benzyl alcohol increased the recovery of radioactivity significantly to 96.7%. As explained in Example 23, improving recovery of radioactivity from the vial is important as it allows use of less radioactivity in the reaction as a whole.

Applicants urge that one skilled in the art reviewing the instant specification would understand that the addition of benzyl alcohol would improve the recovery of radioactivity significantly (e.g. by more than 10%) for radiopharmaceutical compositions of limited solubility. One skilled in the art is well aware of which radiopharmaceutical compositions or radiolabeled

chelators are of limited solubility. Thus, the description is more than adequate to show that the Applicant was in the possession of the instant invention at the time of filing.

Moreover, contrary to the Examiner's assertion the reactants– benzyl alcohol and a radiolabled chelators of limited solubility or a reaction mixture for a radiopharmaceutical composition of limited solubility are described as are the species which achieved the result (e.g. those in Example 23). Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 USC 1nd Paragraph-enablement.

Claims 228-230 were rejected for alleged lack of enablement. The Examiner found that the phrase "water soluble organic compound containing selenium +2" is critical or essential to the practice of the invention, "but not included in the claims(s) is not enabled by the disclosure." The Examiner stated that "[r]eview of the specification (i.e. paragraph [0365] of the published application US 2002/0122768) indicates that the phrase "water soluble aromatic amine" is present in the specification, not "water soluble organic compound". But it is duly noted that in the application as originally filed, the phrase "water soluble organic compound containing selenium +2" is present in the claims. Hence Applicants is respectfully requested to incorporate the necessary phrases in the specification since they are present in the originally filed claims." (Office Action at page 7). Applicants respectfully traverse.

The test for enablement is whether one reasonably skilled in the art could make or use the claimed invention without undue experimentation, based on the disclosure in the application and the information available in the art. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP § 2164.01. The Office must consider many factors for enablement, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01(a).

Applicants respectfully point to the significant guidance and working examples provided in the instant case. Here, claims 228-230 require "a water soluble organic compound containing selenium in the +2 oxidation state" described and enabled in the instant specification. The Examiner is respectfully directed to paragraph [0032] of the instant published application, which discusses water soluble organic compounds wherein the selenium is in the +2 oxidation state:

"In the third approach, formulations contain stabilizers that are water soluble organic selenium compounds wherein the selenium is in the oxidation state +2. Especially preferred are the amino acid compounds selenomethionine, and selenocystein and their esters and amide derivatives and dipeptides and tri peptides thereof, which can either be added directly to the reaction mixture during radiolabeled complex preparation, or following complex preparation. The flexibility of having these stabilizers in the vial at the time of labeling or in a separate vial extends the utility of this invention for manufacturing radiodiagnostic or radiotherapeutic kits".

The Examiner is also directed to paragraphs [0172]-[0173] and [0185]. Indeed paragraph [0185] states:

"Organic compounds containing selenium in the +2 oxidation state: Organic compounds containing selenium in the +2 oxidation state, including selenomethionine and selenomethionine and selenocysteine have not been reported as a radioprotectant for radiopharmaceuticals, nor has cysteine or other organic compounds containing thiols in the +2 oxidation state. Both of these compounds were found to be radioprotectants in their own right, and to have valuable properties if added to a radiolysis stabilizing solution as described in this disclosure".

Moreover, use of water soluble organic compounds containing selenium in the +2 oxidation state is exemplified in the instant Examples 9-11, 21 and 22.

Notably, the test for "undue experimentation" is not merely quantitative, and the time and difficulty experimentation are not determinative. *Wands*, 858 F.2d at 737; MPEP § 2164.06. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance for how the experimentation should proceed. *Wands*, 858 F.2d at 737; MPEP § 2164.06. Where an invention involves biological activity, this itself does not constitute "undue experimentation," particularly where the level of skill is high (as noted in the instant case; *see* Office Action, page 6-7). *Wands*, 858 F.2d at 740.

Furthermore, Applicants need only provide *sufficient* disclosure to teach those of skill in the art how to make and use the claimed invention. MPEP § 2164. The standard does not require thousands of examples or every possible species for the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Thus, the instant application provides considerable guidance and working examples for the instant methods and at the time of filing, one of skill in the art would be able to make, test and use the claimed compounds without undue experimentation. Thus, Applicants urge that the specification provides sufficient enablement for the claimed methods and respectfully request withdrawal of this rejection.

Rejections Under 35 USC 2nd Paragraph

Claims 193, 194, 214, 215, 217 and 219-230 were rejected for alleged indefiniteness. In claims 193, 194, 214, 215, 217 and 219-230 the Examiner found that it was unclear what reactants are present in the reactions. "[I]t is unclear if Applicant is claiming that the instant invention will work in ALL reactions that produce a radiopharmaceutical composition in the presence of benzyl alcohol." (Office Action at page 7). Applicants respectfully traverse.

"The test for definiteness under 35 U.S.C 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification". See MPEP 2173.02, quoting Orthokinetics, Inc. v. Safety travel Chairs, Inc., 806 F. 2d 1565, 1576 (Fed. Cir. 1986).

As explained above in connection with the rejection for alleged lack of written description, Applicants amended claims require a method of significantly increasing recovery of radioactivity from a reaction that produces a radiopharmaceutical composition of limited solubility by adding benzyl alcohol to the reaction mixture that produces the radiopharmaceutical of limited solubility or to the stabilizer solution added to a radiolabeled chelate of limited solubility. As set forth in paragraph [0023] and Example 23 of the instant specification,

Applicants unexpectedly found that addition of benzyl alcohol solubilizes radiopharmaceutical compositions of limited solubility so they remain dissolved in the reaction solution and thus significantly more of these solutions (and the radioactivity they contain) can be recovered from the reaction vial.

Indeed, in Example 23, in the absence of benzyl alcohol only 85.3 % of the radioactivity could be recovered from the vial while addition of benzyl alcohol increased the recovery of radioactivity significantly to 96.7%. One skilled in the art would understand that the addition of benzyl alcohol would improve the recovery of radioactivity significantly (e.g. by more than 10%) for radiopharmaceutical compositions of limited solubility. As one skilled in the art is well aware of which radiopharmaceutical compositions or radiolabeled chelators are of limited solubility, Applicants submit that the claims are sufficiently definite. Moreover, contrary to the Examiner's assertion the reactants present in the reaction– benzyl alcohol and a radiolabeled chelators of limited solubility or a reaction mixture for a radiopharmaceutical composition of limited solubility--are sufficiently definite. Applicants respectfully request withdrawal of this rejection.

Claims 193, 194, 214, 217 and 219-230 were rejected for alleged indefiniteness because the Examiner found that "increasing recovery is unclear and the specification does not provide a standard." Applicants respectfully traverse.

The amended claims require a method of significantly increasing the recovery of radioactivity of a radiopharmaceutical composition of limited solubility using benzyl alcohol. The skilled artisan would understand that what is meant by recovery is the amount of radioactivity that can be removed from the vial when its contents are removed. Some radioactive compounds, especially those of limited solubility, may precipitate out on the walls of the vial over time. When the radiopharmaceutical is removed from the vial the precipitated portion may remain stuck to the vial walls. Thus, if 25% of the radioactivity in a radiopharmaceutical composition containing 200mCi remains deposited on the wall of the vial, only 150 mCi can be recovered. As set forth in Example 23, Applicants have invented a method to reduce the radioactivity that remains deposited on the vial walls and thus increase the recovery of

radioactivity by more than 10% (e.g. 11.4%), which the skilled artisan would understand to be a significant increase in recovery. Thus, Applicants submit that the claim language "significantly increasing recovery" is sufficiently definite.

Claims 221, 223, 224, 226 and 229 were rejected for alleged indefiniteness due to inclusion of the language "analogs and derivatives thereof", "analogs thereof" or "derivatives thereof". Applicants respectfully traverse. Analogs are defined at paragraph [0124] of the instant specification:

"Additionally, analogues of a targeting molecule can be used. These analogues include molecules that target a desired site receptor with avidity that is greater than or equal to the targeting molecule itself. For targeting peptides analogues include muteins, retropeptides or and retro-inversopeptides of the targeting peptide. One of ordinary skill will appreciate that these analogues may also contain modifications which include substitutions, and/or deletions and/or additions of one or several amino acids, insofar that these modifications do not negatively alter the biological activity of the targeting molecules".

Applicants submit that the language "and derivatives" in claim 221 is also sufficiently definite to the skilled artisan; however, solely to expedite prosecution Applicants have deleted this language.

Regarding claim 229, the phrase selenomethionine, selenocysteine and derivatives thereof is defined at paragraph 0172:

"In the third approach, formulations contain stabilizers that are water soluble organic selenium compounds wherein the selenium is in the oxidation state +2. Especially preferred are the amino acid compounds selenomethionine, and selenocysteine and their esters and amide derivatives and dipeptides and tri peptides thereof, which can either be added directly to the reaction mixture prior to or during radiolabeled complex preparation, or following complex preparation. The flexibility of having these stabilizers in the vial at the time of labeling or in a separate vial extends the utility of this invention for manufacturing radiodiagnostic or radiotherapeutic kits. Thus, Applicants submit that claim 229 is sufficiently definite given this definition.

Claim 225 was rejected for alleged indefiniteness as the Examiner found that it is unclear what GRP agonist or peptide Applicant is claiming that confer agonist activity to the desired molecule. GRP agonists and peptides which confer agonist activity are well known in the art and are described at paragraph [0128]:

"The GRP receptor targeting molecule may take the form of an agonist or an antagonist. A GRP receptor targeting molecule agonist is known to "activate" the cell following binding with high affinity and may be internalized by the cell. Conversely, GRP receptor targeting molecule antagonists are known to bind only to the GRP receptor on the cell without stimulating internalization by the cell and without 'activating" the cell. In a preferred embodiment, the GRT receptor targeting molecule is an agonist and more preferably it is a peptide agonist."

Applicants submit that this claim is sufficiently definite in light of this definition.

Claim 222 was rejected for alleged indefiniteness because it is missing claim status. In view of cancellation of claim 222, this rejection is moot and should be withdrawn.

Claim 228 was rejected for alleged indefiniteness because the Examiner found that it was unclear what specific water soluble organic compounds Applicants is claiming that are compatible with the instant invention and yield the desired results. The claim requires a water soluble organic compound containing selenium in the +2 oxidation state. Such compounds are well known to those skilled in the art and, as explained above are defined in paragraphs 032, 0185, 0172-0173 and in the Examples, including Examples 9-11, 21 and 22. Applicants submit that the claim is sufficiently definite and request withdrawal of the rejection.

Rejections Under 35 USC 102 (a)

Claims 193 was rejected under 35 U.S.C. 102 (b) as being allegedly anticipated by Gustafson et al (British Journal of Industrial Medicine, 1985, Vol. 42, page 591-595 – "Gustafson"). The Examiner found that "Gustafson et al disclose the influences of organic solvent mixtures on biological membranes….In particular, Table 3 (page 594) discloses release radioactivity in benzyl alcohol alone and benzyl alcohol and ethanol. The released radioactivity

of benzyl alcohol is disclosed at 5.0 +/- 3.7 and benzyl alcohol and ethanol is 50.9 +/- 9.3. Thus, both Applicant and Gustafson et al disclose an increase of radioactivity recovery resulting from a radiopharmaceutical composition reaction." (Office Action at page 9). Applicants respectfully traverse.

In order to anticipate a claim, a single prior art reference must disclose each and every limitation of the claim. MPEP 2131. As an initial matter the instant claims require a method of significantly increasing recovery of radioactivity from a reaction that produces a radiopharmaceutical composition of limited solubility. However, Gustafson neither teaches or suggests any method involving a radiopharmaceutical composition. Instead it is directed to bacteria labeled with ^{14}C, an isotope that has a very low energy and long half-life and thus is not useful as a radiopharmaceutical. Indeed, this isotope does not have sufficient emission energy to be imaged as a radiodiagnostic or to be useful in radiotherapy. Thus, for this reason alone, Gustafson cannot anticipate the claims.

Moreover, Gustafson actually teaches way from the claimed invention, by establishing that benzyl alcohol alone is not a particularly good solvent for improving radioactivity recovery from the radiolabled bacteria. In Gustafson bacteria were grown in the presence of a radiolabeled fatty acid (^{14}C-oleic acid). After radioactivity had become incorporated into the cell membranes of the bacteria (believed to be primarily as ^{14}C-phosphatidylethanolamine), bacteria were trapped on a 0.45 μM filter, and then treated with various solvents to determine which was most effective at extracting the incorporated radioactivity. Extraction of high amounts of radioactivity would be expected to be related to two processes, a) damage of the cell membrane of the bacteria, and b) extraction of the radiolabeled ^{14}C-phosphatidylethanolamine from the damaged and/or undamaged cells. The following data were obtained.

Table 3 *Release of ^{14}C-radioactivity from radiolabelled E coli incubated with various non-polar solvents, alone or together with ethanol (33%).(Values are mean ± SD of three to six experiments)*

Solvent	*Released radioactivity*	
	Solvent alone	*Solvent + ethanol*
Ethanol	7·0 ± 2·2	—
1-Butanol	14·7 ± 7·4	73·9 ± 7·9
Benzyl alcohol	5·0 ± 3·7	50·9 ± 9·3
Ethyl acetate	ND	45·6 ± 0·9
Toluene	ND	5·2 ± 2·1
Xylene	ND	2·0 ± 1·8
Chloroform	ND	4·7 ± 0·2

ND = Not detectable.

Treatment of the cells with benzyl alcohol alone extracted only 5.0 +/-3.7% of the radioactivity -a poor result. Addition of 33% EtOH to this mixture caused a dramatic increase in the amount of radioactivity obtained, to 50.9 +/- 9.3%. Thus, Gustafson indicates that benzyl alcohol alone is a rather poor solvent for removal/recovery of radioactivity. Consequently, Applicants submit that Gustafson cannot anticipate claim 193 and request withdrawal of this rejection.

Rejections Under 35 USC 103 (a)

Claims 193, 194, 214, 215 and 219-228 were rejected for alleged obviousness over Liu at al US 2002/0122768 ("Liu"). Liu is said to disclose radiopharmaceutical compositions comprising an effective amount of an aromatic stabilizer that may be used in combination with other stabilizers, including benzyl alcohol and ascorbic acid. "Thus a skilled artisan would recognize that radioactivity from the radiopharmaceutical composition reaction would increase because radiolytic degradation of the radiopharmaceutical is inhibited...Hence , both Applicants and Gustafson et al [sic – Liu] disclose an increase of radioactivity recovery resulting from a radiopharmaceutical composition reaction." (Office Action, page 12). Applicants respectfully traverse this rejection.

In order to establish obviousness, it is necessary, *inter alia*, to (i) determine the scope of the prior art and (ii) the differences between the claimed subject matter and that of the prior art.

Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). Furthermore, a *prima facie* finding of obviousness cannot be established when the "improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1739 (2007). A reasonable expectation of success is required. MPEP 2143.02. Unexpected, *i.e.* surprising, results rebut a *prima facie* case of obviousness. MPEP 2144.09.

Liu is directed to an aromatic stabilizer of recited formula for use in stabilizing radiopharmaceutical compositions. This formula does not include benzyl alcohol. Liu teaches that the radiopharmaceutical compositions can optionally include a second stabilizer selected from a group including benzyl alcohol. However, Liu only teaches that the second stabilizer can be used in addition to the claimed aromatic stabilizer to increase the stability of radiopharmaceutical compositions and no data establishing its ability to act as a stabilizer is provided. *See* Liu, paragraph 0053.

As explained above, the instant invention is directed to solving the problem of deposition of radioactivity on vial walls that occurs with radiopharmaceuticals of limited solubility. The claimed solution is to use benzyl alcohol to significantly increase the recovery of radioactivity. Not only does Liu fail to teach or disclose the claimed method, it even fails to identify or discuss the problem solved by the invention. Moreover, Liu neither teaches nor suggests that benzyl alcohol can be used as anything other than a second stabilizer in a stabilizing composition including a claimed aromatic stabilizer. It certainly does not teach or suggest that benzyl alcohol can be used to solubilize a radiopharmaceutical of limited solubility. Thus, Applicants submit that Liu cannot render the claimed invention obvious. Moreover, given Liu's failure to teach or suggest the problem solved by the invention (never mind the claimed solution) and Gustafson's teaching away from use of benzyl alcohol as a solvent for radioactivity, Applicants submit that the claims are patentable over all cited art.

Thus, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Respectfully submitted,

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